UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,138	01/08/2007	Jerome B. Zeldis	9516-352-999	5513

20583 7590 08/26/2008

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
08/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,138	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/24/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-9 are pending and under examination.

Priority

This application is a 371 of PCT/US/2004/037083, filed November 4, 2003, and claims priority to U.S. Provisional Application No. 60/517,405, filed November 6, 2003.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 10/24/2006. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 2 recite a method of treating, managing, or preventing a specific cancer. However, the claims do not recite what the "specific" cancer being treated, managed, or prevented is. As such, it is unclear what cancer is intended to be treated, managed, or prevented.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of thalidomide or a pharmaceutically acceptable salt or sterioisomer thereof, does not reasonably provide enablement for a "*solvate*" of thalidomide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The claims recite administration of a "solvate" of thalidomide. The term "solvate" cover various forms of thalidomide at different proportions of water or solvents. Thus, the scopes of the above claims are unduly broad because solvates encompass thalidomide solvated with any solvent in any ratio of thalidomide to solvent.

The specification does not define what a "solvate" is and it does not provide working examples to guide the skilled chemist to make a solvate of thalidomide. There is no guidance on what proportion of water or solvent to use for obtaining a "solvate". Thus, the specification fails to provide sufficient enablement for making the claimed solvates of thalidomide.

Although it is not unusual to expect a "solvate" of a compound to form, the process for selecting a particular solvate is not standard for all drugs. Furthermore, the teaching of

Vippagunta (Adv. Drug Del. Rev., Vol. 48, (2001), pp. 3-26) flatly states on page 18, section 3.4 the following:

> "Predicting the formation of solvates or hydrates of a compound...is complex and difficult."

Thus, the state of the prior art does not support the broad scope of the above claims.

Even with the advanced training, the skilled clinician would have to engage in extensive research to select a particular "solvate" of thalidomide and determine which solvates, if any, have the therapeutic activity recited in the instant claims.

The process of making a "solvate" is quite unpredictable because it is not possible to predict whether solid solutions will form and at what stoichiometry proportion (*i.e*, one, two, or half a molecule of solvent added per molecule of host). Thus, with such a limited teaching from the specification and the art, the skilled chemist would have to engage in undue experimentation to make and use the claimed "solvate" of thalidomide as recited in the instant claims.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cancer or a disease associated with angiogenesis, does not reasonably provide enablement for managing or preventing cancer or a disease associated with angiogenesis comprising administering thalidomide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to

> practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment, management, or prevention of all cancers and all diseases alleged to be associated with undesired angiogenesis comprising administering thalidomide.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

As illustrative of the state of the art with respect to administering thalidomide to treat cancer, the examiner refers to the teachings of **Bach *et al.*** (Acta Path., 1963, *59*:491-499) (cited by Applicant in IDS filed 10/24/2006), **Gutman *et al.*** (Anticancer Research, 1996, *16*:3673-3677) (newly cited), **DiPaolo** (Cancer Chemotherapy Reports, 1963, *29*:99-102) (cited by Applicant in IDS filed 10/24/2006), **Thomas *et al.*** (Current Opinion in Oncology, 2000, *12*:564-573) (newly cited) and **Grabstald *et al.*** (Clinical Pharmacology and Therapeutics, 1965, *6*:298-302) (cited by Applicant in IDS filed 10/24/2006). All references are cited for evidentiary purposes only.

Bach *et al.* studied the possible antineoplastic effect of thalidomide in experimental mouse models. The reference also discusses a report in which a woman with an X-ray resistant pelvic tumors was treated with thalidomide (400 mg daily). The tumors increased in size during the treatment. Bach *et al.* transplanted NJA tumors (a transplantable leukemia) and PBH tumors (an adenocarcinoma) in mice (page 494). The mice were then treated with varying doses (11.2, 112.0, 560.0 and 1120.0 mg/kg) of thalidomide (page 495). In mice with PBH tumors, all thalidomide treated mice died before controls (pages 496-497). In the NJA implanted mice, there was no significant effect of thalidomide on the survival times of the animals. Further,

histological exam revealed no difference with regard to the extent of the leukemic infiltrations in the organs between treated and untreated mice (pages 496-497). The authors conclude that thalidomide had no antineoplastic effect (page 498).

Gutman *et al.* tested the efficacy of thalidomide in treating solid tumors in mice (Abstract). B16-F10 (melanoma) and CT-26 (colon carcinoma) cells were injected in mice and the mice then received 0.3-1.0 mg thalidomide (*id.*). There was no growth retardation in CT-26 bearing mice or in mice with pulmonary or peritoneal metastases of B16-F10 melanoma (*id.*). All tumors reached maximum size, similar to controls. Further, morphological exam revealed that in both thalidomide and control groups, all mice had developed an intact network of new blood vessels (*id.*). In conclusion, the authors report that the present study did not demonstrate a sustained, reproducible, anti-angiogenic effect of thalidomide in solid tumors growing in mice (page 3676).

DiPaolo also studied the effects of thalidomide in treating standard rat and mouse tumors, including adenocarcinoma, Ehrlich ascites, leukemia, sarcoma, Murphy-Sturm, lymphosarcoma and Walker 256 (Table 1). The daily dose of thalidomide was 500 mg/kg (*id.*). Based on the results of this study, DiPaolo concludes, "thalidomide is ineffective against transplantable cancers" (page 102).

Thus, in three separate studies, thalidomide was ineffective in inhibiting tumor growth in mouse models of cancer, including animal models of blood-borne tumors (*e.g.*, leukemia). Given this information, the skilled artisan would not reasonably expect thalidomide to be effective in broadly preventing and managing cancers or in treating, preventing, or managing other diseases associated with undesired angiogenesis.

Grabstald *et al.* is cited as evidence to support the unpredictability of treating, let alone preventing and managing, cancers in humans using thalidomide. The reference teaches that thalidomide was administered to 71 patients with a wide spectrum of cancers, including multiple myeloma and lymphoma (Abstract; Table I). There was no evidence of an objective response in any cancer except one patient with renal cell cancer (*id.* at page 301). The authors conclude, "further random trials of this [thalidomide] drug against cancer in man are not indicated" (page 301).

Thomas *et al.* provides a review of the current role of thalidomide in cancer treatment. Although the article will not be discussed in detail, several points are pertinent to the present rejection. Firstly, the article states that the first oncology studies of thalidomide were reported in 1965 (Grabstald *et al.*, cited *supra*). Further, another study of 21 patients with various solid tumors who were treated with thalidomide revealed no tumor regressions (page 564). Secondly, several clinical trials of thalidomide have been carried out (pages 566-569). Thalidomide has shown moderate effects in some cancers (gliomas – 2/36 patients had partial response, 2/36 patients had a minor response, and 12/36 had stable disease; Kaposi's sarcoma – 6/17 patients had a partial response, 8/17 patients withdrew from toxicity; renal cell carcinoma – 3/18 patients had partial response) (pages 566-567). However, there were no objective tumor responses in 63 patients with metastatic prostate cancer, no objective responses in 17 patients with melanoma, no objective responses in 12 patients with breast cancer or 19 patients with ovarian carcinoma, and no objective tumor responses in 17 patients with metastatic squamous cell carcinoma of the head and neck (in fact, 94% of patients had progressive disease) (pages 567-568). Thirdly, a summary of FDA new drug applications issued for thalidomide between 1997 and 1998 yielded data on 480 patients treated for breast, CNS, prostate, skin, colon, pancreas and kidney malignancies. Thalidomide was given in doses up to 2400 mg daily. Responses were observed in 36 patients (7.5%), 10 of who had received combination therapy (*i.e.* not thalidomide alone), whereas 53% of patients discontinued therapy because of toxicity (page 568). Thus, it is clear that the treatment of cancer in humans, let alone the management or prevention of cancer, with thalidomide is extremely unpredictable and in the majority of cases completely ineffective.

Thus, a preponderance of evidence suggests that treating tumors with thalidomide, particularly in humans, is extremely unpredictable and in the majority of cases ineffective. While angiogenesis is indeed one mechanism suggested by the prior art to influence tumor growth, the fact that a drug inhibits angiogenesis does not, *a priori*, mean that it will be effective in preventing or managing cancer or treating, preventing, or managing diseases associated with undesired angiogenesis. The prior art clearly shows this to be the case.

There is no example in the prior art of an inhibitor of angiogenesis being an effective prevention of cancer or diseases associated with angiogenesis. Further, Applicant appears to be

claiming a "magic bullet" that can be administered to any patient that will prevent said patient from ever getting any cancer or any disease associated with undesired angiogenesis (e.g, acne, syphilis, Herpes simplex infection, protozoan infection, rheumatoid arthritis, sickle cell anemia, gingivitis, and "wasting") (see claim 7). This "magic bullet" is also alleged to be capable of treating all of the following diseases: diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, mariginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, pvriphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagers disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechet's disease, retinitis, choroiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, rubeosis, ¢ndotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, or 5q- syndrome.

It is entirely unpredictable whether thalidomide will have any therapeutic efficacy in treating, let alone preventing, any of the plethora of diseases and conditions recited in the instant claims. Further, the Examiner is unaware of any small molecule chemical compound that is capable of preventing all cancers as recited in the instant claims.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the prevention and management of any cancer as well as the general treatment, management, and prevention of a plethora of

diseases alleged to be associated with undesired angiogenesis comprising administering thalidomide.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to prevent or manage all of the various cancers claimed, or to treat, prevent, or manage all of the various diseases alleged to be associated with undesired angiogenesis, particularly in humans. The single working example is limited to demonstrating that *in vitro*, thalidomide enhances the degradation of TNF-α mRNA. Although broad doses and administration routes of thalidomide are described in the specification, these doses and administration routes are contemplated to be useful for the treatment of all angiogenic-related conditions. No reasonably specific guidance is provided concerning useful therapeutic protocols for any specific conditions or diseases, particularly the prevention or management of cancer or the treatment, prevention, or management or diseases associated with angiogenesis.

Further, there are no *in vitro* or *in vivo* experimental models of any diseases described, including cell proliferation or animal tumor models. While the administration routes disclosed in the specification are standard routes of administration for therapeutic agents, Applicant has provided no specific administration regimens (*e.g.* timing, specific doses, etc.) necessary to treat, prevent, or manage any specific disease.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that thalidomide could be predictably used to prevent and manage all cancers or to treat, prevent, and manage the claimed diseases alleged to be associated with undesired angiogenesis.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicant has presented a general idea that because thalidomide inhibits angiogenesis it must therefore, *a priori*, be useful in the treatment, management, and prevention of all diseases associated with undesired angiogenesis, including all cancers and diseases not limited to diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, mariginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, pvriphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagers disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechet's disease, retinitis, choroiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, rubeosis, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, or 5q- syndrome.

Given the extremely diverse cancers and diseases encompassed by the claims and the limited examples provided in the specification, the skilled artisan cannot predict what specific cancer or disease may or may not be amiable to treatment, management, or prevention with thalidomide.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 102(a) as being anticipated by **Celgene Corporation** ("Celgene Corporation announces fourth quarter and full year results for 2002", Press Release, January 2003) (cited by Applicants in IDS filed 10/24/2006; Reference C82).

Celgene Corporation teaches that the combination of thalidomide and dexamethasone was administered to 50 patients with newly diagnosed multiple myeloma (page 3). Multiple myeloma is a cancer recited in instant claims 5 and 6 and dexamethasone is an anti-cancer agent as recited in instant claims 8 and 9.

Celgene Corporation additionally teaches that thalidomide was administered to patients with follicular or papillary thyroid cancer as recited in instant claim 5 (*id.*).

The reference thus anticipates the claimed method of treating cancer with thalidomide and thalidomide in combination with an additional anti-cancer agent.

Claims 1-2, 5-6, and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by **Danson *et al.*** (Journal of Clinical Oncology, July 2003, vol. 21, no. 13, pages 2551-2557) (newly cited).

Danson *et al.* teach administration of temozolomide and thalidomide to patients with metastatic malignant melanoma, thus anticipating the claimed method of treating cancer comprising administering thalidomide in combination with another anti-cancer agent (Abstract).

Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by **D'Amato** (USP No. 5,629,327; Issued May 13, 1997) (cited by Applicants in IDS filed 10/24/2006; Reference A64).

D'Amato teaches thalidomide and related compounds inhibit angiogenesis (Abstract) and are used to inhibit unwanted angiogenesis in a human or animal (col. 5, lines 9-11). The invention provides methods for treating diseases mediated by angiogenesis, including solid tumors, leukemia, Kaposi's sarcoma, and diabetic retinopathy as recited in the instant claims (col. 5, lines 15-45). Also see the list of diseases recited at column 14, line 38 to column 15, line 18, which are the same diseases recited in the instant claims. The claims of the D'Amato patent recite methods of treating undesired angiogenesis in a human or animal comprising administering thalidomide.

The reference thus teaches the same method of treating cancer or a disease associated with undesired angiogenesis comprising administering thalidomide as recited in the instant claims.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Andrulis *et al.*** (USP No. 5,731,325; Issued Mar. 24, 1998) (cited by Applicants in IDS filed 10/24/2006; Reference A58).

Andrulis *et al.* teaches methods for the treatment of malignant melanoma comprising administering thalidomide alone or in combination with other anti-melanoma drugs (Abstract; col. 5, lines 5-36). Drugs that are combined with thalidomide include other anti-melanoma agents (*i.e.*, anti-cancer agent) as recited in claim 8, specifically vincristine or dexamethasone as recited in instant claim 9 (col. 6, lines 54-59 and col. 7, lines 12-23).

The reference thus anticipates the claimed methods of treating cancer comprising administering thalidomide alone or in combination with an additional anti-cancer agent.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Andrulis *et al.*** (USP No. 6,140,346; Issued Oct. 31, 2000) (cited by Applicants in IDS filed 10/24/2006; Reference A48).

Andrulis *et al.* teaches methods for the treatment of neoplastic diseases comprising administering thalidomide alone or in combination with other anti-neoplastic agents (Abstract; col. 9, lines 21-25).

Drugs that may be combined with thalidomide include other anti-cancer agents as recited in claim 8, such as vincristine, doxorubicin, melphalan, and dexamethasone as recited in instant claim 9 (col. 10, line 24 to col. 11, line 5).

Also see claim 2 of the Andrulis *et al.* patent, which explicitly claims a method of treating a neoplastic disease comprising administering thalidomide in combination with other alkylating agents selected from the group consisting of mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustin, cisplatin, and carboplatin.

The reference thus anticipates the claimed methods of treating cancer comprising administering thalidomide alone or in combination with an additional anti-cancer agent.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Zeldis *et al.*** (US 2002/0035090 A1; Published Mar. 21, 2002) (cited by Applicants in IDS filed 10/24/2006; Reference A31).

Zeldis *et al.* teach methods for the treatment of cancer comprising administering thalidomide in combination with other anti-cancer agents (Abstract; page 4, [0034]).

Cancers that can be treated by the disclosed method include cancer of the head, neck, eye, mouth, throat, esophagus, chest, bone, lung, colon, rectum, stomach, prostate, breast, ovaries, kidney, liver, pancreas, and brain as recited in instant claims 5 and 6 (page 4, [0035] and page 7, [0063]) as well as Kaposi's sarcoma as recited in instant claims 7 and 8 (page 7, [0063]).

Drugs that may be combined with thalidomide include other anti-cancer agents as recited in claim 8, such as topotecan as recited in instant claim 9 (page 4, [0044]). Also see the

list of anti-cancer drugs that may be used in combination with thalidomide for the treatment of cancer as recited at page 8, [0070].

Also see claim 2 of the Andrulis *et al.* publication, which explicitly claims a method of treating a neoplastic disease comprising administering thalidomide in combination with other alkylating agents selected from the group consisting of mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustin, cisplatin, and carboplatin.

Also see Example 1 of Zeldis *et al.* (pages 14-15) which teaches administration of thalidomide and irinotecan to patients having colorectal cancer.

The reference thus anticipates the claimed methods of treating cancer comprising administering thalidomide alone or in combination with an additional anti-cancer agent.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Govindarajan *et al.*** (US 2002/0035091 A1; Published Mar. 21, 2002) (newly cited).

Govindarajan *et al.* teach methods for the treatment of colorectal cancer comprising administering thalidomide in combination with irinotecan (Abstract; page 3, [0027], [0028], [0032], [0033], and [0034]; page 4, [0037]; page 8, Example 1).

Colorectal cancer is a cancer recited in instant claims 5 and 6 and irinotecan is anti-cancer agent as recited in claim 8 and as explicitly recited in instant claim 9.

Also see Example 1 of Govindarajan *et al.* (page 8, Example 1) which teaches administration of thalidomide (400 mg/day) and irinotecan (325-350 mg/m^2 every 21 days) to patients having colorectal cancer.

The reference thus anticipates the claimed methods of treating cancer comprising administering thalidomide in combination with an additional anti-cancer agent.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Govindarajan *et al.*** (Oncology, 2000, vol. 14, no. 12, suppl. 13, pages 29-32) (newly cited).

Govindarajan *et al.* teach administration of 400 mg/day thalidomide in combination with 300 to 350 mg/m2 irinotecan every 21 days to patients having colorectal cancer (Abstract).

Colorectal cancer is a cancer recited in instant claims 5 and 6 and irinotecan is anti-cancer agent as recited in claim 8 and as explicitly recited in instant claim 9.

The reference thus anticipates the claimed methods of treating cancer comprising administering thalidomide in combination with an additional anti-cancer agent.

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by **Olson *et al.*** (Clinical Pharmacology and Therapeutics, 1965, vol. 6, no. 3, pages 292-297) (cited by Applicants in IDS filed 10/24/2006; Reference C18).

Olson *et al.* teach administration of thalidomide in doses ranging from 4.2 to 354 grams to 21 patients having fourteen different types of cancer (Abstract). The cancers include those cancers as recited in instant claim 5.

The reference thus anticipates the claimed method of administering thalidomide to patients having cancer.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **D'Amato *et al.*** (Seminars in Oncology, 2001, vol. 28, no. 6, pages 597-601) (cited by Applicants in IDS filed 10/24/2006; Reference C04).

D'Amato *et al.* teach that thalidomide has been administered in trials to treat cancer, including glioblastomas, Kaposi's sarcoma, glioma, prostate carcinoma, renal cell carcinoma, and multiple myeloma – all with at least some indication of efficacy (page 598, left column). In addition, D'Amato teaches that thalidomide in combination with irinotecan has produced partial responses in patients with colorectal cancer (id.)

The reference thus anticipates the claimed methods of administering thalidomide alone or in combination to patients having cancer or a disease associated with undesired angiogenesis.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by **Celgene Corporation** ("Celgene Corporation announces third quarter results", Press Release, October 24, 2002) (cited by Applicants in IDS filed 10/24/2006; Reference C79).

Celgene Corporation teaches that they have finalized programs for Thalidomid (thalidomide) in newly diagnosed multiple myeloma and renal cell carcinoma (page 2). In this regard, Celgene teaches a program for comparing thalidomide plus dexamethasone versus dexamethasone alone as induction therapy in patients with multiple myeloma as doses of 200 mg to 400 mg thalidomide. Celgene also teaches a pivotal trial for thalidomide in renal cell carcinoma at doses of 200 mg to 400 mg thalidomide. Multiple myeloma is a cancer recited in instant claims 5 and 6 and dexamethasone is an anti-cancer agent as recited in instant claims 8 and 9.

The reference thus anticipates the claimed method of treating cancer with thalidomide and thalidomide in combination with an additional anti-cancer agent.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by **Steins *et al.*** (Blood, February 2002, vol. 99, no. 3, pages 834-839) (cited by Applicants in IDS filed 10/24/2006; Reference C50).

Steins et al. teach administration of thalidomide to patients having acute myeloid leukemia, thus anticipating the claimed method of treating cancer comprising administering thalidomide (Abstract).

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by **Singhal *et al.*** (N. Engl. J. Med., 1999, vol. 341, pages 1565-1571) (cited by Applicants in IDS filed 10/24/2006; Reference C49).

Singhal *et al.* teach administration of thalidomide to patients having refractory multiple myeloma, thus anticipating the claimed method of treating cancer comprising administering thalidomide (Abstract).

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by **Eisen *et al.*** (British Journal of Chemistry, 2000, vol. 82, no. 4, pages 812-817) (cited by Applicants in IDS filed 10/24/2006; Reference C37).

Eisen *et al.* teach administration of continuous low dose thalidomide to patients having melanoma, renal cell, ovarian, or breast cancer, thus anticipating the claimed method of treating cancer comprising administering thalidomide (Abstract).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 5-6, and 7-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8-11, and 61-62 of copending Application No. 09/853,617. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the '617 application recite administration of thalidomide and topotecan to treat primary cancer, including those cancers recited in the instant claims. Further, topotecan is an anti-cancer agent as recited in instant claim 9.

Although no patent number has been assigned to the '617 application, the Notice of Allowance of claims 1-4, 8-11, and 61-62 was mailed 5/13/2008 and the Issue Fee Payment was

made on 8/13/2008. Accordingly, this rejection is not provisional because claims 1-4, 8-11, and 61-62 of the '617 have in fact been allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614